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Prognostic Value of Exercise Echocardiography in 2,632 Patients ≥65 Years of Age

Adelaide M. Arruda, MD, MS, Mini K. Das, MD, Veronique L. Roger, MD, MPH, FACC, Kyle W. Klarich, MD, FACC, Douglas W. Mahoney, MS, Patricia A. Pellikka, MD, FACC

Rochester, Minnesota

OBJECTIVES We sought to determine the prognostic value of exercise echocardiography in the elderly.

BACKGROUND Limited data exist regarding the prognostic value of exercise testing in the elderly, a population which may be less able to exercise and is at increased risk of cardiac death.

METHODS Follow-up (2.9 ± 1.7 years) was obtained in 2,632 patients ≥65 years who underwent exercise echocardiography.

RESULTS There were 1,488 (56%) men and 1,144 (44%) women (age 72 ± 5 years). The rest ejection fraction was 56 ± 9%. Rest wall motion abnormalities were present in 935 patients (36%). The mean work load was 7.7 ± 2.3 metabolic equivalents (METs) for men and 6.5 ± 1.9 METs for women. New or worsening wall motion abnormalities developed with stress in 1,082 patients (41%). Cardiac events included cardiac death in 68 patients and nonfatal myocardial infarction in 80 patients. The addition of the exercise electrocardiogram to the clinical and rest echocardiographic model provided incremental information in predicting both cardiac events (chi-square = 77 to chi-square = 86, $p = 0.003$) and cardiac death (chi-square = 71 to chi-square = 86, $p < 0.0001$). The addition of exercise echocardiographic variables, especially the change in left ventricular end-systolic volume with exercise and the exercise ejection fraction, further improved the model in terms of predicting cardiac events (chi-square = 86 to chi-square = 108, $p < 0.0001$) and cardiac death (chi-square = 86 to chi-square = 99, $p = 0.004$).

CONCLUSIONS Exercise echocardiography provides incremental prognostic information in patients ≥65 years of age. The best model included clinical, exercise testing and exercise echocardiographic variables. (J Am Coll Cardiol 2001;37:1036–41) © 2001 by the American College of Cardiology

It has been estimated that the proportion of the U.S. population ≥65 years of age will increase progressively and, in the year 2050, will comprise 79 million people (1). In the elderly, the prevalence of coronary artery disease is high, and cardiovascular disease is the leading cause of death. However, elderly patients may be less able to exercise (2), which makes identification of high risk patients more difficult in this age group.

Limited data on the prognostic value of exercise testing in elderly patients are available (2). The purposes of the present study were to determine the prognostic value of exercise electrocardiography and exercise echocardiography in patients ≥65 years of age and to assess the incremental value of exercise electrocardiography and exercise echocardiography in predicting cardiac events in this population.

METHODS

Patients. From January 1990 to December 1995, 6,420 patients were referred for clinically-indicated exercise echocardiography. Of the patients, 234 (4%) had inadequate echocardiographic images (no echocardiographic evidence of ischemia and two or more segments not visualized), and 142 patients (2%) refused to participate in the study. Of the remaining 6,044 patients, 2,716 were at least 65 years of age. Follow-up data were obtained in 2,632 of these patients (97%); these comprise the study group. No statistically significant differences were present in these patients, as compared with patients without follow-up.

Exercise echocardiography. All patients underwent symptom-limited treadmill exercise testing according to: 1) the Bruce protocol in 2,181 (83%); 2) the Naughton protocol in 259 (10%); and 3) the modified Bruce protocol in 192 (7%). Work load was measured by metabolic equivalents (METs). Two-dimensional echocardiographic images were obtained from the parasternal and apical windows before and immediately after exercise (3).

Both quad-screen digitized and videotape-recorded images were used for interpretation of all studies (4). The ejection fraction (EF) at rest was measured using a previously validated modification of the method of Quinones et al. (5) or by visual estimation (6); after exercise, it was measured by visual estimation. Regional wall motion was assessed semiquantitatively by an experienced echocardiographer (7) who had no knowledge of the clinical information. Wall motion at rest and with exercise in each of 16 segments was scored 1 through 5 (8). The wall motion score

From the Division of Cardiovascular Diseases and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota. Dr. Arruda was supported by grants from the CAPES Foundation (Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), Brasília, Brazil, and from the Mayo Foundation.

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Abbreviations and Acronyms

CI	=	confidence interval
ECG	=	electrocardiogram
EF	=	ejection fraction
LA	=	limits of agreement
LVESV	=	left ventricular end-systolic volume
METs	=	metabolic equivalents
MI	=	myocardial infarction
RR	=	risk ratio
WMSI	=	wall motion score index

index (WMSI) was determined at rest and peak exercise as the sum of the segmental scores divided by the number of visualized segments. The development of new or worsening wall motion was considered indicative of ischemia. A wall motion abnormality present at rest and unchanged with exercise was classified as "fixed." The percentage of segments that were abnormal was calculated as follows: abnormal (ischemia or fixed abnormality) segments divided by the number of visualized segments, multiplied by 100%. The change in left ventricular end-systolic volume (LVESV) from rest to exercise was determined by visual estimation, using a side-by-side comparison of rest and exercise digitized images, and was recorded as normal (decrease in LVESV) or abnormal (no change or increase) (9).

Interobserver and intraobserver variabilities. To assess the interobserver variability, two independent observers assessed the EF and LVESV responses in a sample of 20 tests randomly selected according to a systematic sampling framework to represent a range of responses and image qualities. Intraobserver variability was determined similarly in a sample of 20 tests. A third independent observer measured EF and LVESV at rest and during exercise by using the modified biplane Simpson method (Image Vue, Nova Microsonics, Allendale, New Jersey).

Follow-up. Follow-up was obtained by mailed questionnaires and scripted telephone interviews. The events were verified by contacting the patients' physician and by reviewing medical records and death certificates. The end points were cardiac events, including myocardial infarction (MI) and cardiac death. Sudden death occurring without another explanation was included as cardiac death. Patients who had coronary revascularization before other events were eliminated from the study at the time of revascularization.

Statistical analysis. Continuous variables were reported as the mean value ± SD, and categoric variables as percentages. The level of agreement (intraobserver, interobserver and intermethod) for exercise EF was assessed by the method of Bland and Altman. Cohen's kappa statistic was used to assess the level of agreement regarding the subjective categorization of the LVESV response to exercise. Survival free of the end point of interest was estimated by using the Kaplan-Meier method. The association between the clinical and exercise echocardiographic variables and the end points was assessed in the Cox proportional hazards framework by using the variables listed in Table 1. The variables were selected in a stepwise forward selection manner with entry and retention set at a significance (p) level of 0.05 and summarized as the risk ratio (RR) with corresponding 95% confidence interval (CI).

Table 1. Univariable Predictors of Cardiac Events (Cox Regression Analysis) in Patients Undergoing Exercise Stress Echocardiography

Variable	RR	95% CI	p Value
Clinical data			
Previous MI	2.69	1.95–3.72	0.0001
Diabetes mellitus	2.05	1.36–3.09	0.0006
Age*	1.79	1.22–2.37	0.005
Previous CABG	1.87	1.32–2.66	0.0004
Male gender	1.64	1.16–2.33	0.005
Q-waves on rest ECG	2.10	1.49–2.95	0.0001
Rest echocardiographic data			
EF†	0.60	0.54–0.66	0.0001
Rest WMSI	3.62	2.67–4.91	0.0001
Exercise ECG data			
Exercise-induced angina	1.57	0.99–2.50	0.005
Positive exercise ECG	1.05	0.72–1.55	0.79
Work load‡	0.85	0.80–0.92	0.001
Exercise echocardiographic data			
Percent abnormal segments with exercise§	6.63	4.20–10.5	0.0001
Abnormal LVESV response	3.57	2.56–5.00	0.0001
Exercise WMSI‖	3.57	2.70–4.73	0.0001
Change in WMSI‖	2.89	1.66–5.02	0.0002
Exercise EF†	0.66	0.60–0.74	0.0001
Change in EF†	0.66	0.54–0.74	0.0001

*Per decade. †Per 10-U change in ejection fraction (EF). ‡Per 1 MET change in work load. §Per 10% abnormal segments. ‖Per 1-U change in wall motion score index (WMSI). Variables that were not predictive included angina, hypertension and previous coronary angioplasty.

CABG = coronary artery bypass graft surgery; CI = confidence interval; LVESV = left ventricular end-systolic volume; RR = risk ratio; other abbreviations as in Table 1.

The incremental value of exercise echocardiographic information over clinical, rest echocardiographic and exercise electrocardiographic (ECG) data was assessed in three modeling steps. The first step consisted of fitting a multivariable model of only clinical and rest echocardiographic data. The variables selected from the first step were then used as baseline risk factors, and exercise ECG variables were added in a stepwise forward selection manner. The predictive accuracy of each modeling step was assessed by using a modified concordance statistic (C-index) for censored data (10). This statistic estimates the probability of correctly ordering the event times of two randomly selected subjects given their respective model covariates. A significant improvement in model prediction was based on the likelihood ratio statistic, which follows a chi-square distribution.

RESULTS

Study group. The study group consisted of 1,488 men (56%) and 1,144 women (44%); their mean age was 72 ± 5 years (range 65 to 91). Cardiovascular risk factors included: hypercholesterolemia in 1,438 patients (55%), hypertension

Table 2. Exercise Test Characteristics

Variable	n (%)
Indication for test	
Chest pain or dyspnea	1,629 (62%)
Known coronary artery disease	730 (28%)
Risk stratification before noncardiac surgery	136 (5%)
Multiple risk factors	71 (2.5%)
Recent MI	66 (2.5%)
Exercise ECG results	
Negative	1,257 (48%)
Positive	619 (23%)
Nondiagnostic	756 (29%)
Exercise echocardiographic results	
Normal	1,133 (43%)
Ischemia	557 (21%)
Fixed abnormality	417 (16%)
Fixed abnormality and ischemia	525 (20%)

ECG = electrocardiographic; MI = myocardial infarction.

in 1,351 (51%), a family history of premature coronary artery disease in 899 (34%), diabetes mellitus in 288 (11%) and smoking in 173 (7%). Of the patients, 629 (24%) had a history of typical angina, 453 (17%) had previous coronary artery bypass graft surgery, 308 (12%) had previous coronary angioplasty and 628 (24%) had previous MI. The baseline ECG was abnormal in 1,696 patients (64%): 1,165 (44%) had ST-T wave changes, 528 (20%) had a previous Q-wave MI and 329 (13%) had other abnormalities.

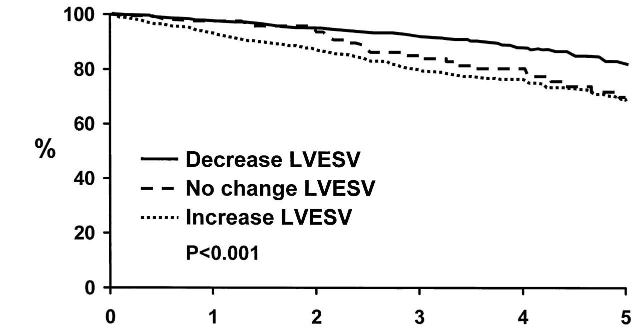
Exercise echocardiography. The patients' characteristics and exercise test results are summarized in Table 2. The mean work load was 7.7 ± 2.3 METs for men and 6.5 ± 1.9 METs for women (p = 0.0001). The WMSI was 1.2 ± 0.4 at rest and 1.3 ± 0.4 with exercise. The EF increased from 56 ± 9% to 62 ± 13% with exercise (p = 0.001). The EF increased in 1,988 patients (76%). The LVESV did not decrease in 676 patients (26%).

Interobserver and intraobserver variabilities and volumetric data. There was 100% intraobserver agreement (kappa = 1.0 ± 0.0009) and 85% interobserver agreement (kappa = 0.8 ± 0.12) regarding the subjective interpretation of the LVESV response to exercise. Volumetric assessment revealed a decrease in LVESV in 18 (95%) of 19 tests that were subjectively classified as a normal LVESV response, and an increase or lack of change in 15 (81%) of 21 tests subjectively classified as abnormal. The volumetric assessment for the two groups was significantly different (−14 ± 13 vs. 2 ± 25 ml, p = 0.001). The intraobserver and interobserver differences in the subjective assessment of

Table 3. Multivariable Predictors of Cardiac Events in Patients Undergoing Exercise Echocardiography

Variable	RR	95% CI	p Value
Abnormal LVESV response	1.98	1.32–2.96	0.0004
Diabetes mellitus	1.83	1.21–2.78	0.004
Previous MI	1.56	1.09–2.24	0.02
Age	1.48	1.08–2.02	0.01
Exercise EF	0.78	0.69–0.90	0.0003

Abbreviations as in Tables 1 and 2.



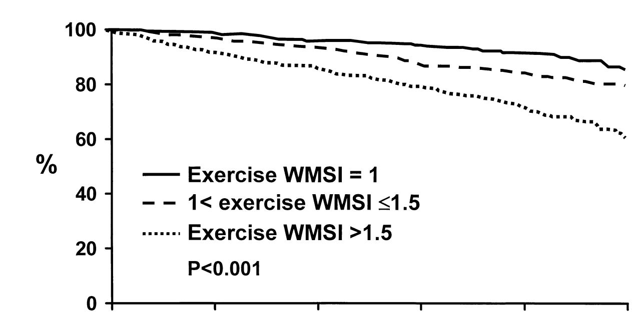
No. at risk	0	1	2	3	4	5
——	1,959	1,772	1,327	827	485	262
– –	447	369	278	185	106	64
······	226	165	120	76	53	31

Figure 1. Survival free of cardiac events: effect of exercise LVESV response. An increase or lack of decrease in LVESV with exercise was associated with more cardiac events. LVESV = left ventricular end-systolic volume.

exercise EF were 0.1 ± 2.3 (95% limits of agreement [LA] −5%, 5%) and 0.7 ± 3.8 (95% LA −5%, 10%), respectively. The mean difference between the subjective interpretation of the exercise EF and the volumetric assessment was 0.3 ± 3.3 (95% LA −6%, 7%).

Outcomes. During a median follow-up period of 2.6 years (mean 2.9 ± 1.7), there were 148 cardiac events, including cardiac death in 68 patients and nonfatal MI in 80 patients. Of the patients, 274 underwent revascularization before any cardiac event. For cardiac death, the estimated one- and five-year event-free survival rates were 99.5% and 95.4%, respectively. For cardiac events, the corresponding rates were 98.8% and 88.9%.

Predictors of cardiac events. The univariate associations with cardiac events are shown in Table 1. Multivariable predictors of cardiac events are reported in Table 3. When exercise EF and LVESV responses were excluded from consideration, the significant predictors were diabetes mellitus (RR 1.71 [CI 1.13 to 2.58], p = 0.004), previous MI (RR 1.56 [CI 1.09 to 2.24], p = 0.012), exercise WMSI



No. at risk	0	1	2	3	4	5
<1	1,094	1,008	749	460	274	150
1-1.5	898	795	613	407	237	135
>1.5	640	503	363	221	133	72

Figure 2. Survival free of cardiac events: effect of exercise WMSI. More events were observed with a higher exercise WMSI. WMSI = wall motion score index.

Table 4. Multivariable Predictors of Cardiac Death in Patients Undergoing Exercise Echocardiography

Variable	RR	95% CI	p Value
Age	2.02	1.23–3.31	0.005
Q-wave on rest ECG	1.72	1.05–2.84	0.03
Work load	0.84	0.75–0.95	0.004
Exercise EF	0.63	0.54–0.73	0.0001

Abbreviations as in Tables 1 and 2.

(RR 2.78 [CI 2.03 to 3.81], p = 0.001) and work load (RR 0.89 [0.83 to 0.95], p = 0.001). Figures 1 and 2 depict the univariate impact of LVESV response and exercise WMSI on survival free of cardiac events.

For cardiac death, the multivariable predictors are reported in Table 4. When exercise EF and LVESV responses to exercise were not considered, exercise WMSI (RR 3.48 [CI 2.25 to 5.38], p = 0.001), age (RR 1.97 [CI 1.22 to 1.39], p = 0.006), presence of Q-waves on the rest ECG (RR 1.76 [CI 1.06 to 2.90], p = 0.03) and work load (RR 0.81 [CI 0.72 to 0.92], p = 0.0003) were predictors of cardiac death.

To determine whether the prognostic ability of the final models changed relative to the patient's age, models with and without interactions of age and the final models with the linear predictor were fitted. The 1° of freedom test values for the change in model chi-square were 0.73 (p = 0.39) for "hard" cardiac events, including MI and cardiac death, and 0.71 (p = 0.40) for all cardiac events.

Incremental value of exercise echocardiography. Figure 3 (left) illustrates the incremental value of exercise electrocardiography and exercise echocardiography in predicting cardiac events. Significant clinical factors consisted of age, previous MI, diabetes mellitus and rest WMSI, which provided a C-index of 69%. After forcing these clinical variables into the model, work load (p = 0.003) and exercise-induced angina (p = 0.04) added residual prognostic information. When work load was added to the model, exercise-induced angina was no longer significant. The C-index of this model was 70%. After forcing the clinical variables and work load into the model, all of the exercise echocardiographic variables listed in Table 1 had significant residual prognostic effects. Of these, an abnormal LVESV response (p = 0.0001) contributed the most to the previous model; the C-index was 72%. When exercise EF and LVESV response data were excluded, a change in WMSI (p = 0.001) had the greatest impact and similar predictive accuracy.

Figure 3 (right) illustrates the incremental models for cardiac death. The clinical and exercise ECG variables selected were the same as those for cardiac events. Of the exercise echocardiographic variables, the percentage of abnormal segments at exercise was the only variable that did not have a statistically significant residual impact on outcome (p = 0.054). Of the remaining variables, a change in EF (p = 0.0001) had the greatest residual impact. After excluding exercise EF and LVESV response data, a change in WMSI (p = 0.01) had the greatest impact on survival free of cardiac events. The corresponding C-indexes were 78%, 81% and 82% for the three modeling steps.

DISCUSSION

Incremental value of exercise ECG and exercise echocardiogram. In this study of 2,632 patients ≥65 years of age, both the exercise ECG and the exercise echocardiogram provided significant incremental value, as compared with the clinical and rest echocardiographic variables, for predicting cardiac death and cardiac events. Exercise EF was an independent predictor of both cardiac death and cardiac events. An abnormal LVESV response to exercise was an independent predictor of cardiac events.

It has been reported that for patients who can exercise, exercise testing should be the test of choice over pharmacologic stress testing (11,12). The present study included a large population of elderly patients who could exercise. These patients were not limited by peripheral vascular atherosclerosis, lung disease, osteoarticular abnormalities or

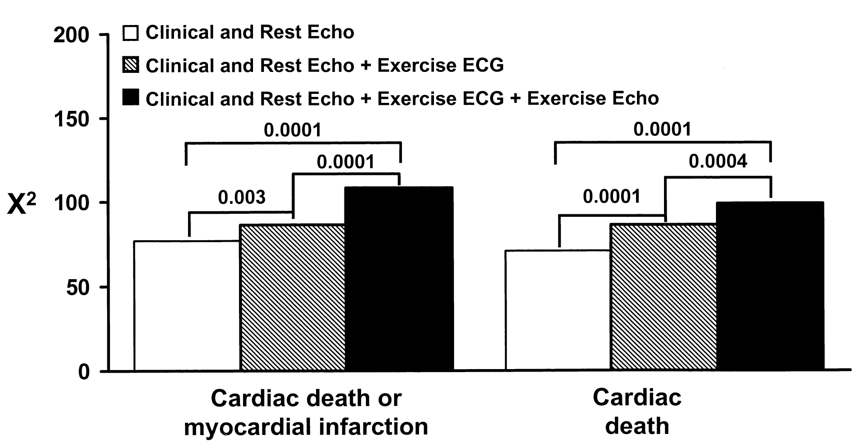


Figure 3. Incremental value of exercise electrocardiography and exercise echocardiography (Echo) in predicting cardiac events **(left)** and cardiac death **(right)**. The addition of exercise ECG variables to the clinical and rest echocardiographic models significantly improved the models. The addition of exercise echocardiographic variables further improved both models.

other diseases that frequently promote disabilities in the elderly. In this elderly population, exercise echocardiography had incremental value additional to the clinical variables of age, diabetes mellitus and previous MI and additional to the exercise ECG.

Of the exercise ECG variables, work load was the most important in predicting both cardiac events and cardiac death. A positive exercise ECG and angina were not predictive. Similarly, in a previous study of patients undergoing treadmill exercise testing, a higher work load was associated with a reduction in the risk of cardiac events and all-cause mortality (13). In a previous study of patients with normal exercise echocardiography, inadequate work load was an independent predictor of cardiac events (14).

Exercise echocardiographic predictors of events. Studies in elderly patients enduring pharmacologic stress have reported that the presence of abnormal results predicted cardiac events (15,16). In our series, we not only classified the results of exercise echocardiography as positive or negative, but also considered additional variables including WMSI, the percentage of segments that were abnormal and changes in LVESV and EF. Among patients with established coronary artery disease, rest left ventricular dysfunction has been described as a predictor of prognosis (17). In our study population, rest WMSI contributed to the clinical model but was not significant when exercise echocardiographic variables were included.

In the present study, an abnormal exercise LVESV response and exercise EF were independent predictors of cardiac events. This is not surprising, as previous studies using stress echocardiography (18) have shown that the abnormal LVESV response to stress was associated with significant coronary disease. In previous studies using radionuclide ventriculography, a low exercise EF was associated with the presence of extensive coronary artery disease (19,20) and was a predictor of cardiac events (21). Limacher et al. (22) described an abnormal exercise EF response using both echocardiography and radionuclide ventriculography in patients with multivessel coronary artery disease; good agreement was noted for both techniques. Our study is the first, to our knowledge, to describe exercise EF, as measured by echocardiography, as an independent predictor of cardiac events. In our study population, exercise WMSI was an independent predictor of cardiac events if the variables of abnormal LVESV and exercise EF were not considered. These variables are similar, for they both reflect the extent and severity of infarction and ischemia. Thus, in addition to information on exercise capacity and segmental wall motion, prognostically important information on the global ventricular response to exercise can be obtained with exercise echocardiography.

Study limitations. The limitations of our study include the absence of a control group of patients <65 years of age. However, when the multivariable model was adjusted according to age, the results were unchanged. The exercise EF and LVESV responses were subjectively assessed. However, we observed good intraobserver and interobserver agreement in estimating both the EF and LVESV responses; there was also good agreement with volumetric assessment. The LVESV response has been previously been described by Chuah et al. (9) as a predictor of cardiac events in patients who underwent dobutamine stress echocardiography. The exercise echocardiographic results were used in managing patients; this may have reduced the prognostic value of the test. Only MI and cardiac death were considered as end points, because the decision for revascularization might have been influenced by the test results. Lastly, follow-up could be obtained in only 97% of patients. However, patients unavailable for follow-up did not differ in terms of clinical or exercise echocardiographic variables.

Conclusions. In this population of 2,632 patients aged ≥ 65 years, exercise electrocardiography, especially work load, had incremental value, as compared with clinical and rest echocardiographic variables, in identifying patients at risk of cardiac events. However, the best model for predicting cardiac events or cardiac death included the results of exercise echocardiography.

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Reprint requests and correspondence: Dr. Patricia A. Pellikka, Mayo Clinic, Division of Cardiovascular Diseases and Internal Medicine, 200 First Street SW, Rochester, Minnesota 55905. E-mail: pellikka.patricia@mayo.edu.

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